CLAIMS

What is claimed is:

1. A method of modifying a biological molecule by formation of a C-O bond, comprising the steps of contacting a biological molecule which is a substrate for a polypeptide selected from the group consisting of:

(a) a polypeptide comprised by an amino acid sequence set forth in SEQ ID NO. 3;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence set forth in SEQ ID NO. 2; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 2 and capable of C-O bond formation;

with said polypeptide whereby said polypeptide modifies the biological molecule by formation of a C-O bond.

2. A method according to claim 1 further comprising the step of contacting the biological molecule modified by the polypeptide recited in claim 1 with a second polypeptide selected from the group consisting of:

(a) a polypeptide comprised by an amino acid sequence set forth in SEQ ID NO. 5;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence set forth in SEQ ID NO. 4; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 4 and capable of C-O bond formation;

whereby said second polypeptide further modifies the biological molecule by formation of a C-O bond.

3. A method according to claim 1 wherein the C-O bond formed is between the biological molecule and a second biological molecule, said second biological molecule also a substrate for the polypeptide.

4. A method according to claim 1 wherein said contacting is in a host cell.

5. A method according to claim 4 wherein said host cell is a bacterium.

6. A method according to claim 4 where the host cell is a eukaryotic cell selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

7. A method according to claim 4 wherein said biological molecule is an exogenously supplied substrate.

8. A method according to claim 1 wherein the contacting is *ex vivo*.

9. A method according to claim 1 wherein said method produces a macrotetralide or a macrotetralide analogue.

10. A method of catalyzing a C-O bond between biological molecules, comprising the steps of contacting biological molecules which are substrates for at least one polypeptide capable of catalyzing C-O bond formation between said biological molecules and encoded by a nucleic acid set forth in SEQ ID NO. 1 or a nucleic acid hybridizing under stringent conditions thereto, with said polypeptide whereby said polypeptide catalyzes C-O bond formation between the biological molecules.

11. A method according to claim 10 wherein said contacting is in a host cell.

12. A method according to claim 11 wherein said host cell is a bacterium.

13. A method according to claim 11 wherein said host cell is a eukaryotic cell selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

14. A method according to claim 11 wherein at least one of said biological molecules is an exogenously supplied substrate.

15. A method according to claim 10 wherein the contacting is *ex vivo*.

16. A method according to claim 10 wherein said method produces a macrotetralide or a macrotetralide analogue.

17. A method of producing a macrotetralide or a macrotetralide analogue, comprising the steps of contacting biological molecules that are substrates for at least one polypeptide selected from the group consisting of:

(a) a polypeptide encoded by an amino acid sequence set forth in SEQ ID NO. 3 or 5;

(b) a polypeptide encoded by a nucleic acid comprising a nucleotide sequence set forth in SEQ ID NO. 2 or 4; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 2 or 4 and capable of C-O bond formation;

with said polypeptide under conditions such that the polypeptide catalyzes a C-O bond between the biological molecules and a macrotetralide or macrotetralide analogue is thereby synthesized; and

recovering said macrotetralide or macrotetralide analogue.

18. A method according to claim 17 wherein said method is carried out in a host cell and at least one biological molecule is an exogenously supplied substrate.

19. A method of preparing a hybrid enzyme comprising the step of positioning in a hybrid enzyme at least one catalytic domain capable of catalyzing C-O bond formation between biological molecules, said catalytic domain encoded by a polypeptide selected from the group consisting of:

(a) a polypeptide encoded by an amino acid sequence set forth in SEQ ID NO. 3 or 5;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence set forth in SEQ ID NO. 2 or 4;

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 2 or 4 and capable of C-O bond formation.

20. A method of preparing a megasynthetase comprising the step of positioning in a megasynthetase at least one module including a polypeptide capable of catalyzing C-O bond formation between biological molecules, said polypeptide selected from the group consisting of:

(a) a polypeptide encoded by an amino acid sequence set forth in SEQ ID NO. 3 or 5;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence set forth in SEQ ID NO. 2 or 4; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 2 or 4 and capable of C-O bond formation.

21. A method of catalyzing C-O bond formation between biological molecules, comprising steps of contacting biological molecules that are substrates for a polypeptide selected from the group consisting of:

(a) a polypeptide comprised by an amino acid sequence set forth in SEQ ID NO. 3;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence set forth in SEQ ID NO. 2; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 2 and capable of C-O bond formation;

with said polypeptide whereby said polypeptide catalyzes C-O bond formation between the biological molecules.

22. A method according to claim 21 wherein said method is performed in a host cell and at least one of the biological molecules is an exogenously supplied substrate.

23. A method of catalyzing C-O bond formation between biological molecules, comprising steps of contacting biological molecules that are substrates for a polypeptide selected from the group consisting of:

(a) a polypeptide comprised by an amino acid sequence set forth in SEQ ID NO. 5;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence set forth in SEQ ID NO. 4; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 4 and capable of C-O bond formation;

with said polypeptide whereby said polypeptide catalyzes C-O bond formation between the biological molecules.

24. A method according to claim 23 wherein said method is performed in a host cell and at least one of the biological molecules is an exogenously supplied substrate.

25. A method of chemically modifying a biological molecule by formation of a C-O bond, comprising contacting a biological molecule that is a substrate for a polypeptide selected from the group consisting of:

(a) a polypeptide encoded by an amino acid sequence set forth in SEQ ID NO. 3 or 5;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence identical to or isolated from SEQ ID NO. 1, 2 or 4;

(c) a polypeptide encoded by a nucleic acid encoding an amino acid sequence set forth in SEQ ID NO. 3 or 5; and

(d) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 1, 2 or 4;

with said polypeptide whereby said polypeptide chemically modifies the biological molecule by formation of a C-O bond.